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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
08/393,066	02/23/1995	JOHN H. WOLFE	PENN:0065	1030

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/393,066	Applicant(s) WOLFE ET AL.	
	Examiner Deborah Crouch, Ph.D.	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

In response to the remand from the Board of Appeals and Interferences, mailed January 17, 2002, the finality of the office action mailed September 13, 1996 is removed. The amendment filed December 17, 1997 has been entered. Prosecution on the merits of pending claims 1-9 resumes with this office action.

The arguments presented in applicant's Reply Brief, filed September 22, 1997 are answered below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-9 are drawn to a method of stably expressing a selected DNA sequence in the central nervous system of a mammal, comprising administering to the mammal a neurotropic virus which infects cells of central nervous system of the mammal, the vector containing a selected DNA sequence operatively linked to a selected promoter so that the selected DNA sequence is stably expressed by infected central nervous system cells, to a method of stably expressing β-glucuronidase in the brain of a mammal comprising administering to the mammal a neurotropic viral vector which infects cells of the brain of the mammal, said vector being and HSV-1 vector containing a DNA sequence encoding β-glucuronidase operatively linked to a LAT promoter, so that the infected brain cells stably express β-glucuronidase.

While the claimed invention requires only stable expression of the selected DNA sequence, the specification provides no use for mere stable expression. The specification is very clear that the purpose of the delivery method to produce a gene therapy (specification, page 2, line 3 to page 3, line 17; page 8, lines 9-13; page 9, line 34 to page 10, line 9; page 16, lines 1-17 and page 20, lines 7-10). At each of these citations, the specification discloses that the method can be used to deliver genes to the CNS to treat a variety of diseases such as Parkinson's Disease and Lesch-Nyhan Disease. The specification does not disclose a use for the claimed method of delivery absent a treatment or therapeutic effect. As the artisan reads the specification to gain guidance on using of an invention, the artisan would see only that the claimed method has a use as a gene therapy. The art does not provide guidance to other uses for in vivo gene delivery absent a therapy. Thus, the claims are not enabled when read in view of the specification. However, applicant should point to page and line number where non-therapeutic uses are disclosed.

At the time of filing, gene therapy was not developed sufficiently that the mere showing of delivery of a gene to a particular tissue would have been viewed as enabling gene therapy. To achieve a therapeutic effect, an amount of a neurotropic viral vector would need to be delivered to the appropriate tissue and expressed sufficiently to provide an alleviation of some symptoms associated with a particular disease.

The artisan would not have considered the specification as enabling as the specification fails to provide sufficient guidance methods of stably expressing a DNA sequence of interest in the CMS of a mammal such that such expression would result in a therapeutic effect. Several references that summarize the art at the time of filing indicate that vector; vector delivery and extent of expression were critical limitations to gene therapy. Verma states that the Achilles heel of gene therapy is gene delivery, and that the

problem lies in the inability to deliver gene efficiently and obtain sustained expression (see Verma, page 239, col. 3, parag. 1). Science News Report states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models (Science 269, page 1050, col. 2, parag. 1, lines 6-15). Anderson states that in situ therapy, as contemplated in the specification by the direct administration of the gene to synovial cells, is hampered by effect ways for implanting corrected genes into various organs, as the genes are not expressed sufficiently to produce sufficient quantities of protein (Anderson (September 1995) Scientific American, 124-126 and 128). Blau states that expression and delivery are seen as the hurdles yet to be overcome for successful gene therapy (Blau (Nov. 2, 1995) The New England J. Med., page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Thus, for the general concept of gene therapy, with claim 1 as an example, the art at the time of filing taught that gene therapy was unpredictable.

In addition, the art at the time of filing teaches with regards to HSV-1 vectors, a neurotropic virus, teaches that the use of HSV-1 vectors in gene therapy protocols was unpredictable. In experiments with first generation HSV vectors, such as those specifically taught in the present specification, gene transfer and transient expression were readily obtainable, but that expression of the DNA sequence of interest was not for a sufficient length of time for effective treatment of neurodegenerative diseases (Fink, page 284, abstract). Further, HSV vectors applied to gene therapy protocols exhibited a residual toxicity resulting from non-replicating vectors and silencing DNA sequence expression from persisting latent HSV genomes in neurons (Fink, page 284, abstract). In rats and mice infected with HSV mutants with reduced cytotoxicity, reporter gene expression was shown to transiently peak 2 days after infection and then becoming undetectable one-week post-

inoculation (Fink, page 288, col. 3, lines 2-8). Others acknowledged the potential use of HSV as gene therapy vectors, but state that the wide spread use of HSV will be restricted until problems concerning the spread of the vector are solved and cytotoxic functions of the virus removed from the vector (Blomer, page 1398, col. 1, parag. 1, line 10 to col. 2, line 4). Eck further states with regards to HSV that the advantages of the vector are countered by difficulty in rendering a viral preparation totally free of replication-competent virus and the eliciting of a potent immune response that are toxic to the infected cell (Eck, page 89, col. 1, parag. 1, lines 9-13). Additionally, it logically follows that if the initial administration of an HSV vector causes a host immune response, subsequent administrations of the virus will be less effective because of a second immune response. With specific regards to an HSV-1 vector expressing β-glucuronidase from the LAP1 promoter, the number of cells expressing the enzyme decreased over time (Fink, page 288, col. 3, lines 6-14). Also, when a HSV-1 construct comprising a cDNA encoding β-glucournidase was administered to MPS VII mice via corneal abrasion, glucuronidase positive staining cells were identified (Wolfe, page 381, col. 2, parag. 2). However, in these experiments, quantative measurements of β-glucuronidase enzymatic activity could not be made because there was too little enzyme for the analysis (Wolfe, page 383, col. 1, parag. 1, lines 7-12). Reference is made that the HSV-1 vector regulating expression from a LAT promoter demonstrates the feasibility of using the vector in gene therapy protocols, but it is also stated that "two few cells have been corrected at this stage to alter the disease phenotype" (Wolfe, page 383, col. 2, lines 1-7). Thus for these reasons the present, the art at the time of filing found gene therapy using an HSV vector or an HSV vector regulating expression form a LAT promoter to be unpredictable.

As the art fails to supply the necessary teachings, it is incumbent on the specification to do so. While the specification need not disclose that which is know in the art at the time of filing, the corollary, the specification need to discloses that which is not known in the art at the time of filing, applies. While the skill level in gene therapy is considered to be high, the skilled artisan would need guidance on treatment protocols to achieve a therapeutic result from the method of delivery.

The guidance provided in the specification is not seen as sufficient to enable a gene therapy method using the vectors claimed. Applicant has not shown that the claimed method can deliver and express a gene sufficiently to cause the amelioration of symptoms associated with a disease. Applicant has not provided guidance as to which promoters would regulate expression sufficiently to achieve a therapeutic effect. The achieving of such expression levels is necessary requirement for gene therapy. Examples 4 and 5 (specification, pages 25-26) teach that the administration, by corneal abrasion, of an HSV vector comprising the DNA sequence for β- glucuronidase operatively linked to the HSV LAT promoter to adult MPS VII mice results in the detection of β-glucuronidase in brain and trigeminal ganglia (a facial nerve) of the mice. However, the mice, which are models for mucopolysaccharidosis VII due to mutations in their GUSB gene, are not described as showing any alleviation of symptoms associated with the disorder due to the treatment. The specification states that the expression of the GUSB gene for 4 months in brain and trigeminal ganglia re presents increases the therapeutic presence of ameliorative enzymes for a lysosomal storage disease (specification, page 26, lines 2-6). However, there is no evidence that the level of expression achieved, which was not specifically stated, correlates to a treatment for mucopolysaccharidosis VII or any other CNS associated disorder. The

specification provides no guidance as to routes of delivery, promoters or neurotropic viral vectors to enable a therapy. It is noted that Wolf, discussed above and an inventor of the present claims, uses the same vector as applicant, and showed the same results. Wolf as stated above states that gene therapy using HSV vectors, and for the correction of mucopolysaccharidosis VII was not predictable at the time of filing.

Therefore, as the specification provides no guidance over than that provided by the art, and the art's clear comments that gene therapy using any vector system, an HSV vector or an HSV vector regulating expression of a DNA sequence of interest was enabled at the time of filing, to implement the presently claimed invention would require the skilled artisan to engage in an undue amount of experimentation without a predictable degree of success.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Palella et al (1989) Gene 80, 137-144.

Palella teaches the infection of mouse brains by intracranial injection of an HSV-1 vector comprising a DNA sequence encoding human hprt operably linked to an HSV-1 thymidine kinase promoter (page 138, col. 2, parag. 4 and page 139, col. 1, parag. 1). Analysis of the brain extracts demonstrated the presence of human hprt DNA sequences, indicating expression of the selected DNA sequence operably linked to a selected promoter (page 143, col. 2, parag. 4). Palella also teaches that expression was observed up to 5 days

after inoculation, indicating that the expression observed was not transient. Thus, Palella clearly anticipates the invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Palella et al (1989) Gene 80, 137-144 and Dobson et al (1989) J. Virol. 63, 3844-3851 in view of Nishimura et al (1986) Proced. Natl. Acad. Sci. 83, 7292-7296.

Palella teaches the infection of mouse brains by intracranial injection of an HSV-1 vector comprising a DNA sequence encoding human hprt operably linked to an HSV-1 thymidine kinase promoter (page 138, col. 2, parag. 4 and page 139, col. 1, parag. 1). Analysis of the brain extracts demonstrated the presence of human hprt DNA sequences, indicating expression of the selected DNA sequence operably linked to a selected promoter (page 143, col. 2, parag. 4). Dobson teaches the delivery of the rabbit ß-globin gene to the peripheral nervous system (PNS) of mice where expression of the ß-globin gene is regulated by the HSV-1 latency promoter (page 3850, col. 1, parag. 4, lines 1-6, page 3847, figure 5). The HSV-1 vector is administered by foot pad injection which is a peripheral inoculation (page 344, col. 2, parag. 1, lines 4-6). Palella and Dobson do not teach the delivery to the CNS or the delivery of β- glucuronidase operatively or tyrosine hydroxylase linked to a promoter. However, Nishimura teaches the DNA sequence for β-glucuronidase (page 7294, figure 3). Palella offers motivation in stating that the system that they describe demonstrates transfer and expression of human gene sequences in brain after an in vivo

infection with recombinant HSV-1, but that there are problems with the system (page 143, col. 1, parag. 4). Further motivation is found in Dobson's teachings that HSV can produce latent infections in both the PNS and the CNS, and that the latency activated promoter, the LAT promoter, is active in such infections (page 3844, col. 1, parag. 1, lines 1-7). Thus given the teachings of Palella that HSV-1 can successfully transfer a human gene and express the gene in infected mouse brains, of Dobson that an HSV-1 vector delivers a gene of interest to the PNS and regulates expression of the gene from the LAT promoter, and that HSV inherently infects both the PNS and CNS and of Nishimura teaching a DNA sequence encoding human β-glucuronidase, it would have been obvious to the ordinary artisan had at the time of filing to deliver any gene of interest, such as one encoding human glucuronidase, to the CNS by administering the vector of Dobson. Absent results to the contrary, the ordinary artisan at the time of filing would have had a reasonable expectation of success in delivering, and expressing, a gene of interest by administering an HSV-1 vector comprising a gene of interest operatively linked to the LAT promoter. Methods for the insertion of DNA sequence of interest, as described in Nishimura, into recombinant HSV-1 vectors ,as described in Palella Dobson, would have been within the scope of skills of the ordinary artisan at the time of the instant invention. Dobson also teaches that three HSV-1 strains have been sequenced in the latency region, and that they have the same structure, one of which is HSV-1 strain 17syn+ (page 3844, col. 1, parag. 2). Thus absent results to the contrary, all strains of HSV-1 would contain the LAT promoter at the same location on the viral genome so that the teachings of Dobson could be applied to each HSV-1 strain. Thus for gene delivery to the CNS, Palella and Dobson in view of Nishimura offers sufficient teachings and motivation for the ordinary artisan to make and use the claimed invention at the time of filing.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
October 9, 2002